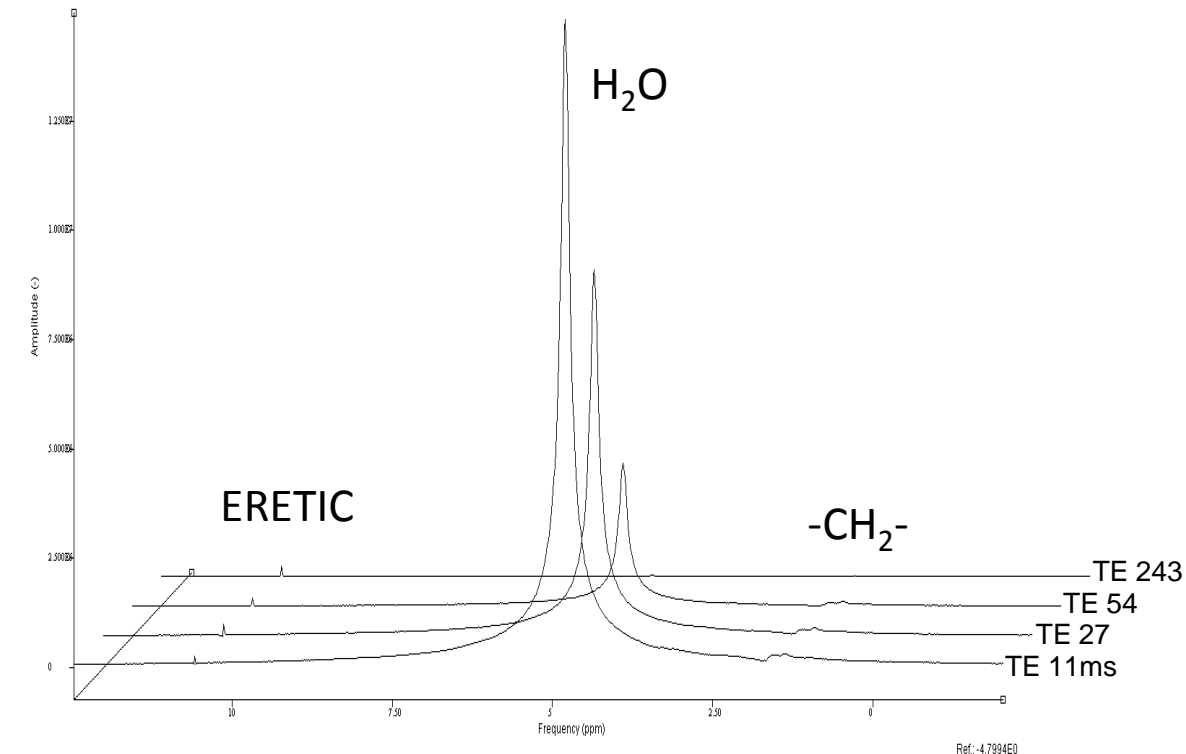


# Quantitative MRI of In Vivo Water and Lipid Concentrations with the ERETIC Method

Eric Baetscher<sup>1</sup>, Thomas M Barbara<sup>1</sup>, Manoj Sammi<sup>1</sup>, Krista Vandeborne<sup>2</sup>, Glenn Walter<sup>2</sup>, and William D Rooney<sup>1</sup>

## Synopsis

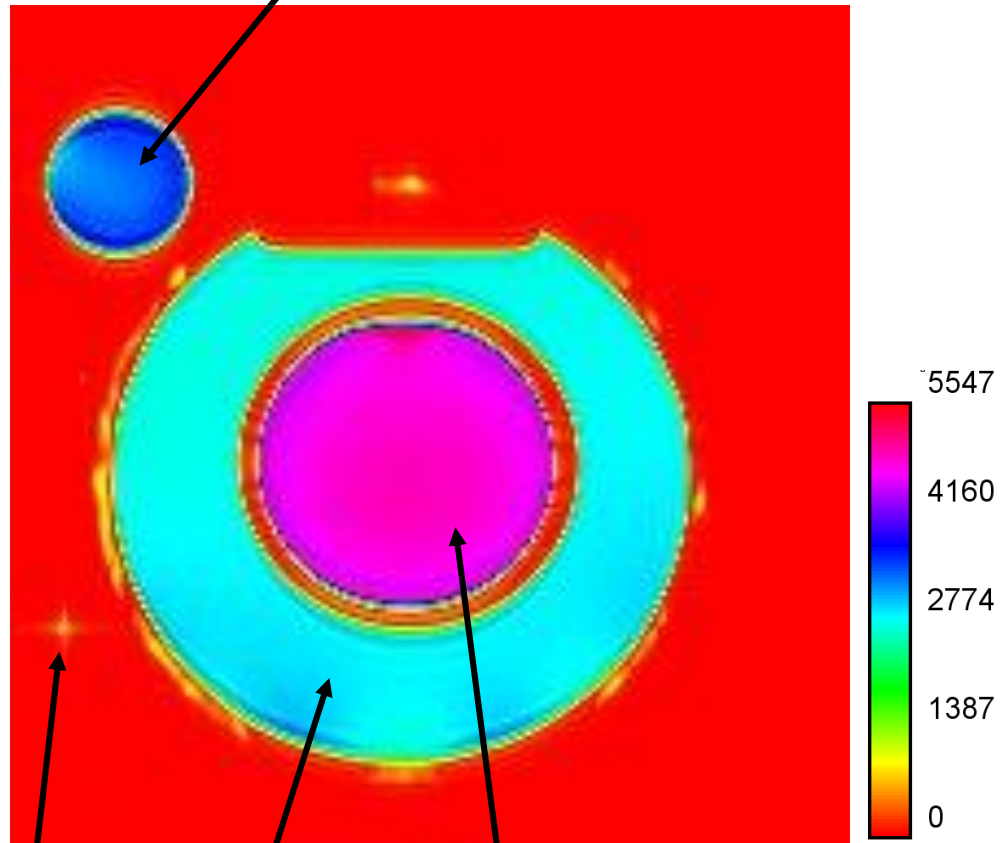
- A synthetic radio-frequency (RF) signal is received along with the  $^1\text{H}$  magnetic resonance (MR) signal in magnetic resonance imaging (MRI) and in vivo MR spectroscopy (MRS) and is used as a stable reference to determine absolute tissue water and lipid quantities.
- We show application of this ERETIC method (electronic reference to access in vivo concentration) to musculoskeletal imaging, with the potential to better track disease progression in Duchenne Muscular Dystrophy (DMD), and other muscle pathologies.



<sup>1</sup>Advanced Imaging Research Center, Oregon Health & Science University, Portland, OR, United States;

<sup>2</sup>Department of Physical Therapy, University of Florida, Gainesville, FL, United States

30% Safflower Oil,  
70% water / gelatin



ERETIC  
signal

100%  
Soybean Oil

30 mM CuSO<sub>4</sub>  
in H<sub>2</sub>O

Calibration phantom  $M_0$  map, with three materials  
of known composition and ERETIC signal

## Purpose

- **The ERETIC technique** (electronic reference to access in vivo concentration)<sup>1</sup> is a **convenient and advantageous alternative to other MRI receiver calibration methods such as phantom replacement or coincident fiducial phantoms.**
- We demonstrate some of the capabilities of ERETIC in the quantification of the water and lipid components of leg muscle.
- Such calibration could improve existing biomarkers that rely upon detection of relative differences between endogenous compounds, such as the measure of muscle fat-fraction in Duchenne Muscular Dystrophy (DMD)<sup>2</sup>.

## Background

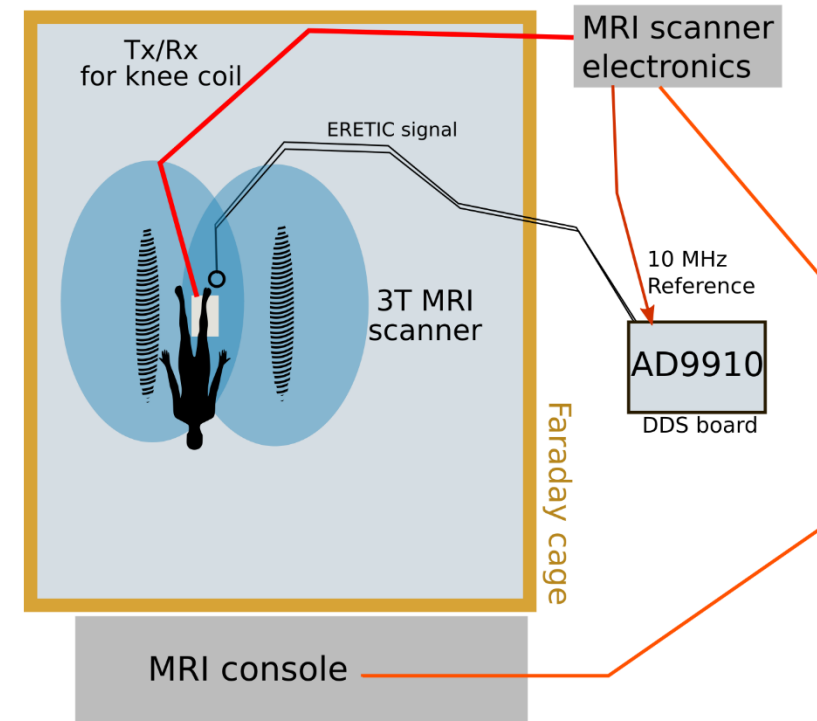
- MRI/S involve transmission and reception of RF signals.
  - RF transmission is carefully calibrated for a number of reasons.
  - Achieving the nominal flip-angle of the nuclear magnetization is crucial to reproducible image signal to noise and contrast.
  - Receiver calibration and stability are subject to less scrutiny. The primary reason for this is that MRI evaluation principally is qualitative in nature. As quantitative approaches become the standard, receiver calibration issues must be addressed.
- Traditional calibration techniques used for absolute quantitation include<sup>3</sup>:
  - Phantom replacement
    - Limitations: Receiver characteristics could change between the calibration phantom measurement and the sample of interest measurement, due to gain, scaling, or coil loading
  - Coincident fiducial phantoms
    - Limitations: Coil placement and image coverage

## ERETIC Technique

- Initial calibration step is required.
  - A phantom with known concentrations is imaged with the ERETIC signal acquired along with the MR signal from the phantom.
  - The amplitude ratio between the ERETIC signal and the per-voxel MRI signal is constant for a given pulse sequence, set of relaxation times ( $T_1$  and  $T_2$ ), and molar concentration.
- The pulse sequences used for the study must match those used in the calibration step. Relaxation times can either be matched between phantom and subject, or  $T_1$  and  $T_2$  maps can be generated to correct for relaxation time differences.

## Methods

- MR data were acquired on a 3-Tesla (3T) Siemens TIM Trio MR instrument<sup>†</sup>.
- The ERETIC signal was generated with a direct digital frequency synthesis (DDS) board<sup>‡</sup>. The ERETIC signal frequency and amplitude were adjustable with provided software.
- A 250-mL Florence-flask filled 5mM Gadoteridol in  $d_5H_2O$  solution was used as a calibration phantom.



Schematic of the basic elements of the ERETIC setup:

- The reference signal from the DDS board is fed through a patch-panel into the Faraday shielded MR scanner room with RG-174 cable.
- Cross diodes to ground provide transmit / receive isolation for the ERETIC circuit.
- An impedance-matched loop antenna in a fixed position with respect to the MRI coil propagates the signal into the room.

<sup>†</sup>(Erlangen, Germany) Later data were acquired on a 3T Siemens Prisma instrument. <sup>‡</sup>(AD9910 evaluation board, Analog Devices, Norwood, MA).

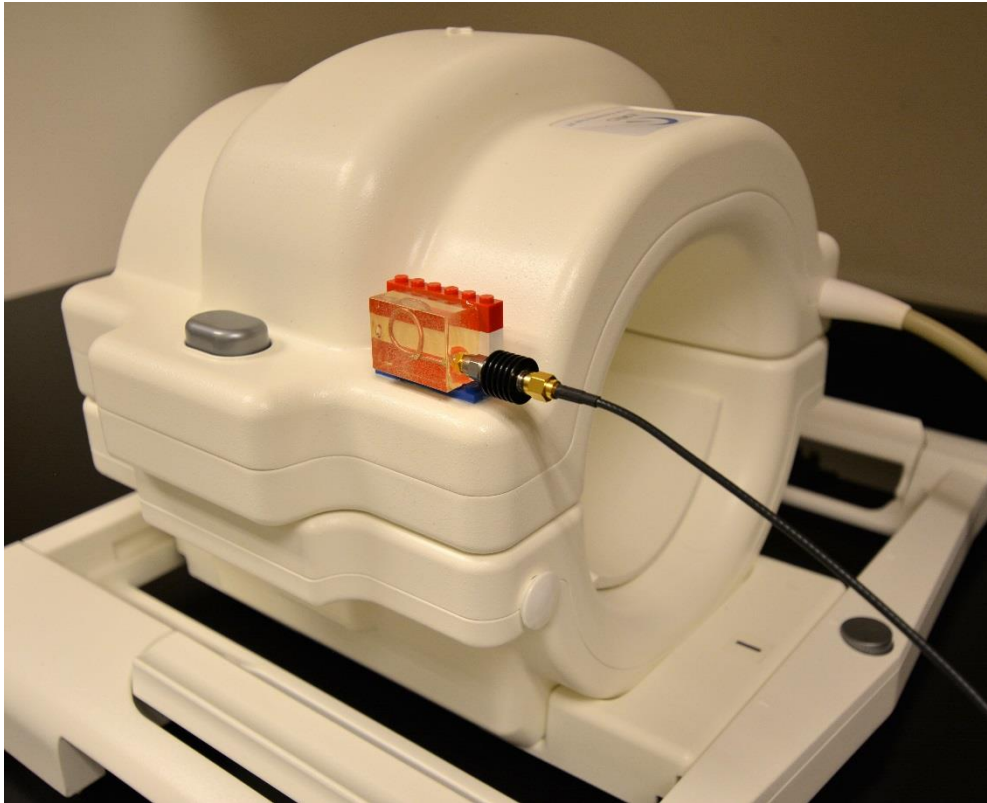


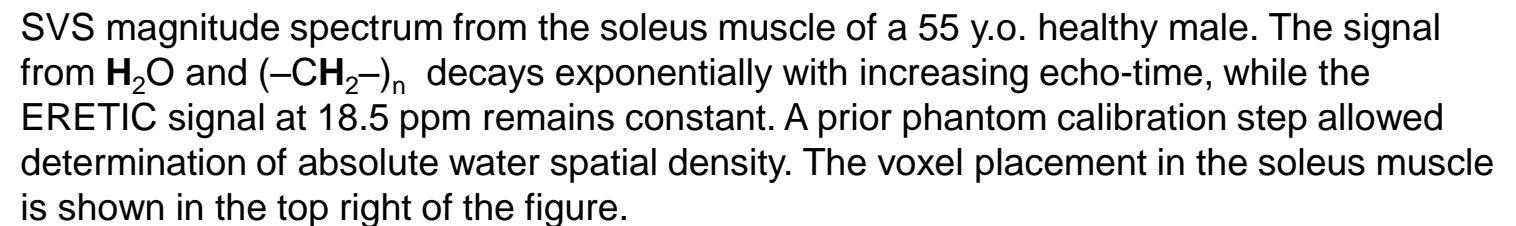
Image showing the Quality Electrodynamics (QED) Tx/Rx circularly-polarized extremity RF coil with attached ERETIC loop antenna and cabling.

## Methods (continued)

Two MR acquisitions were used for the present analysis:

1. A 2D multi-slice spin-echo multi-echo (SE-ME) imaging sequence with 16 echo-times (20 – 320 ms) and a 3000 ms repetition time (TR)
2. A single-voxel spectroscopy acquisition with 16 echo-times (STEAM, TE = 11 – 288 ms, TR = 9000 ms).

The ERETIC signal was frequency modulated to appear at 18.5 ppm in the SVS acquisition and at the corner of the field-of-view in the SE-ME sequence.

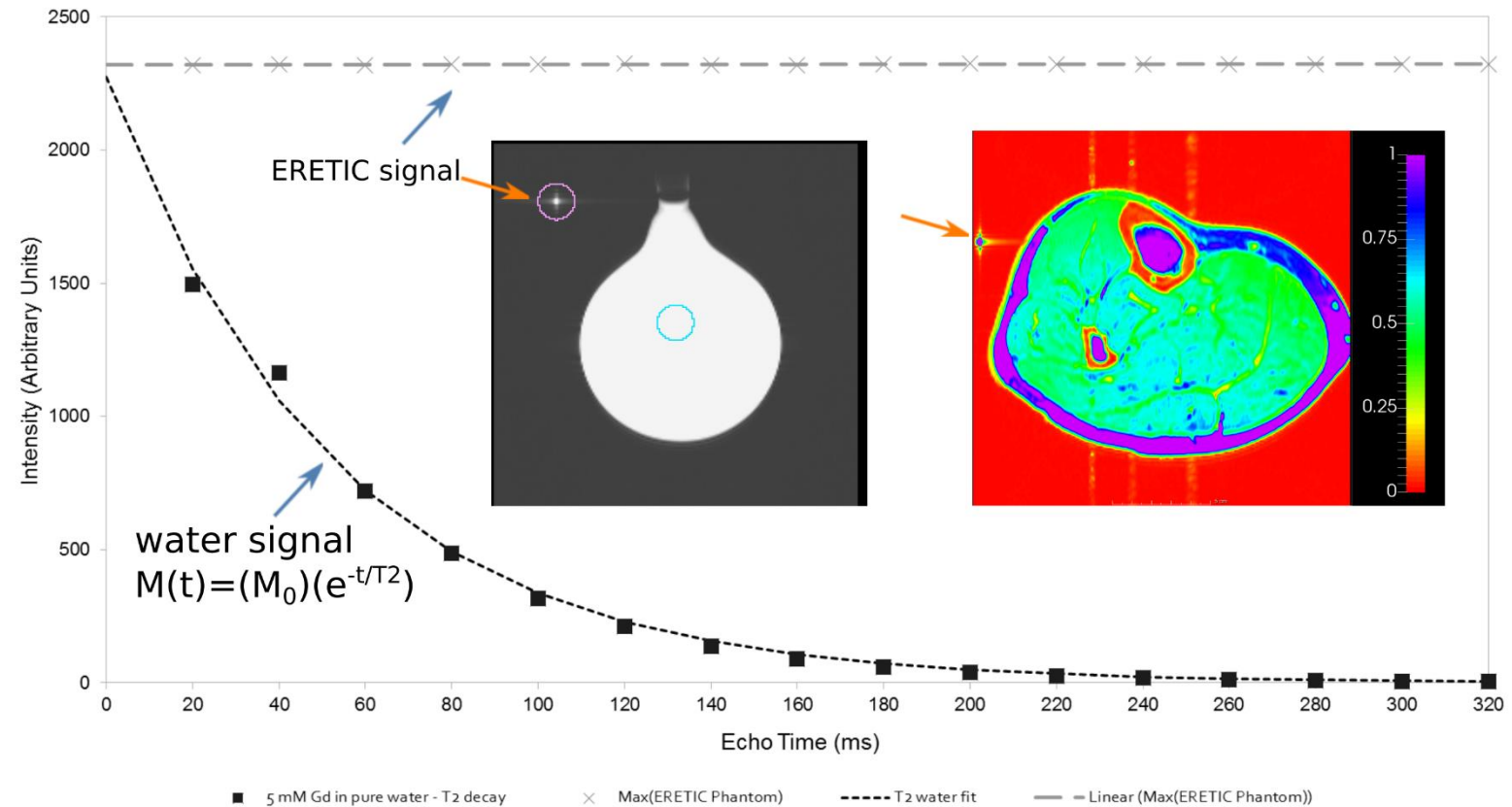




## Results (continued)

For the multi-echo MRI acquisitions, we demonstrate the generation of a quantitative proton-density map with values referenced to the water phantom. In soleus muscle, the mean value was 0.790 with standard deviation of 0.079. Use of the  $M_0$  map derived from  $T_2$  fitting is an advantage of this approach.

Stability of the ERETIC signal amplitude in the multi-echo acquisition was found to have a coefficient of variation (CV) of 0.3% for the phantom acquisition and 0.6% for the leg acquisition.



Results from the MRI T2 SE-ME sequence. The T2 decay plot for the calibration phantom was used to determine the reference value for pure water relative to the ERETIC signal. The parameter map on the right was derived from the  $M_0$  map of the lower-leg of a 60 y.o. male. Its values correspond to an ERETIC-normalized proton density map, and a similar approach combined with the Dixon technique for fat and water separation is a promising alternative method.

## Discussion

- Amplitude stability of the ERETIC signal was excellent. If the stability of the ERETIC signal is comparable or better than the scanner transmit stability, then the MR image intensity due to receiver configuration and variability can be corrected to within the overall variance of the system taken as a whole.
- This application of the ERETIC method has potential to track changes in tissue where absolute quantification of compounds is confounded by changes in the amount of material that is not readily detectable with MRI.
- In the case of DMD, fibrotic tissue with very short T2 values may replace muscle tissue and confound absolute measures of water and lipid. The ERETIC approach has the potential to detect these otherwise hidden changes.
- The ERETIC technique provides the ability to routinely quantify MR signals without cumbersome and error prone phantom approaches and has the potential to add considerable value to the MR exam.
- Possible improvements to the procedure could include:
  - Combination with the Dixon method for lipid/water separation, requires phase synchronization with MR system.
  - Software integration with the vendor MRI acquisition interface to simplify reference signal placement in image space
  - Placement of the ERETIC signal in the frequency-oversampled portion of k-space
  - Use of a virtual phantom (ViP) technique where the k-space representation of a desired shape is synthesized and played-out in synchrony with the MRI pulse sequence.



## Acknowledgements

Grant support:

NIH R01 AR056973, NIH R01 AR065943, NIH R01 NS040801, NIH S10OD018224,  
UL1 RR024140-04S1

## References

1. Akoka S, Barantin L, Trierweiler M. Concentration Measurement by Proton NMR Using the ERETIC Method. *Anal Chem* 1999; 71:2554-2557.
2. Triplett, W. T. et al. Chemical shift-based MRI to measure fat fractions in dystrophic skeletal muscle: MR Measurements of Fat Fraction in Dystrophic Muscles. *Magn Reson Med* 2014; 72: 8–19.
3. de Graaf RA . *In Vivo NMR Spectroscopy*. John Wiley & Sons, Ltd, 2007, pp 466-472.
4. Ward, S.R., Lieber, R.L. Density and hydration of fresh and fixed human skeletal muscle. *J Biomech* 2005; 38: 2317–2320.
5. Franconi F, Chapon C, Lemaire L, Lehmann V, Barantin L, Akoka S. Quantitative MR renography using a calibrated internal signal (ERETIC). *Magn Reson Imaging* 2002; 20: 587-592.
6. Michel N, Akoka S. The application of the ERETIC method to 2D-NMR. *J Magn Reson* 2004; 168: 118-123.
7. Le Grand F, George G, Akoka S. How to reduce the experimental time in isotopic  $^2\text{H}$  NMR using the ERETIC method. *J Magn Reson* 2005; 174: 171-176. Marro KI, Lee D, Shankland EG, Mathis CM, Hayes CE, Amara CE, Kushmerick MJ. Synthetic signal injection using inductive coupling. *J Magn Reson* 2008; 194: 67-75.
8. Desal H, Pineda Alonso N, Akoka S. Electronic reference for absolute quantification of brain metabolites by  $^1\text{H}$ -MRS on clinical whole-body imaging. *J Neuroradiol* 2010; 37: 292-297.